Remarks

I. Status of the Claims

The forgoing amendments do not add new matter, and their entry and consideration are respectfully requested. These amendments are sought to place the claims into condition for allowance or into better form for consideration on appeal.

By the forgoing amendments, claims 36-39, 42, 51, 54, 69, 90, 93, 105, 116, 117 126, 129, 141, 152, 153, 158, 160, 161, 162, 188, 189, 211, 214, 215 and 219 have been amended. Support for these amendments can be found throughout the specification. Specifically, support for the amendments to claims 36-39, 42, 116, 117, 152, 153, 158, 160, 161, 162, 188, 189, 214 and 215 can be found in these claims as originally filed; at page 16, lines 26-31; and at page 18, lines 24-29. Support for the amendments to claims 51, 54, 90, 93, 126 and 129 can be found in these claims as originally filed. Support for the amendments to claims 69, 105 and 141 can be found in these claims as originally filed, and in the specification at page 21, lines 23-29. Support for the amendment to claim 211 can be found throughout Example 6, at pages 47-51. The amendment to claim 219 is made to provide the proper dependency of this claim. Upon entry of the foregoing amendments, claims 35-225 are pending in the application, with claims 35, 78, 115, 151, 159, 187 and 213 being the independent claims.

II. Summary of the Office Action

In the Office Action dated April 9, 2003, the Examiner has made five rejections of and one objection to the claims. Based on the following remarks, Applicants respectfully

request that the Examiner reconsider all outstanding rejections and objections and that they be withdrawn.

III. The Rejection Under 35 U.S.C. § 102(b) Over Johnson

In the Office Action at pages 4-6, the Examiner has maintained the rejection of claims 35, 36, 40-71, 74, 77, 158, 159 and 163-186 under 35 U.S.C. § 102(b), as being anticipated by Johnson *et al.* WO 93/19172 (hereinafter "Johnson"). Applicants respectfully traverse this rejection.

Present claim 35 (and hence claims 36, 40-71, 74, 77 and 158 that depend ultimately therefrom and that are also rejected over Johnson) recites a method of producing a nucleic acid molecule, comprising: providing a first nucleic acid molecule comprising at least a first gene or portion thereof and at least a first recombination site; providing a second nucleic acid molecule comprising at least a second gene or portion thereof and at least a second recombination site; and forming a mixture *in vitro* between the first and second nucleic acid molecules and at least one recombination protein, under conditions sufficient to cause recombination *in vitro* between the first and second recombination sites, thereby producing a third nucleic acid molecule in which the first and second genes or portions thereof are operably linked to form a functional gene. Similarly, present claim 159 (and hence claims 163-186 that depend ultimately therefrom and that are also rejected over Johnson) recites a method of producing a nucleic acid molecule comprising, providing a first nucleic acid molecule comprising at least one promoter located adjacent to at least a first recombination site; providing a second nucleic acid molecule comprising at least one gene or portion

thereof located adjacent to at least a second recombination site; and forming a mixture *in vitro* between the first and second nucleic acid molecules and at least one recombination protein, under conditions sufficient to cause recombination *in vitro* between the first and second recombination sites, thereby producing a third nucleic acid molecule in which the at least one promoter and the at least one gene or portion thereof are operably linked.

Thus, the claims rejected over Johnson all are drawn to methods in which the recombination reaction takes place *in vitro*, *i.e.* outside of host cells. The Examiner contends that Johnson teaches that recombination reactions may be performed *in vitro*. Applicants respectfully disagree with this contention, and note that Johnson only mentions *in vitro* Cre-catalyzed recombination in passing (*see, e.g.*, Johnson at page 21, lines 9-11). However, Johnson provides no experimental details to support such a statement, and all of the protocols in the Examples in Johnson are limited to *in vivo* recombination wherein the recombination takes place inside of host cells (*see, e.g.,* Johnson in Example 1, at page 45, and in Example 2, at page 51). Applicants therefore respectfully assert that Johnson is deficient and cannot be relied upon to reject the claimed invention under 35 U.S.C. § 102(b).

Indeed, the disclosure in Johnson does not enable one of ordinary skill to make and use the presently claimed *in vitro* methods. At best, Johnson only refers in passing to *in vitro* recombination, while only exemplifying intracellular recombination methods, and provides no details on how *in vitro* recombination could or should be accomplished. The Examiner is directed to Applicants' specification where some of the difficulties with performing *in vitro* recombination are discussed, outlining the need for the present invention (see present specification at page 6, lines 1-16). While Johnson briefly acknowledges

recombination *in vitro*, in light of the difficulties associated with performing these types of reactions, the disclosure of Johnson clearly *would not* be considered by one of ordinary skill to enable such methods. Indeed, without additional disclosure in Johnson, one of ordinary skill would have to undertake undue experimentation to devise the presently claimed *in vitro* recombination methods, determining, for example, the proper amounts of nucleic acids and recombination proteins, buffer conditions and incubation times. All of these details are provided in the present specification, but are lacking in Johnson. Hence, Johnson does not enable the claimed invention.

As the Federal Circuit has held, a claim can only be anticipated by a publication if the publication describes the claimed invention with sufficient enabling detail to place the public in possession of the invention. *See In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985); *see also PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1566 (Fed. Cir. 1996) ("To anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter."). For the reasons discussed in detail above, Applicants respectfully submit that Johnson does not provide an enabling disclosure of the present invention. Hence, in view of *Donohue* and *PPG Industries*, Johnson does not anticipate claims 35, 36, 40-71, 74, 77, 158, 159 and 163-186. Reconsideration and withdrawal of the rejection of these claims under 35 U.S.C. § 102(b) over Johnson are respectfully requested.

IV. The Rejection Under 35 U.S.C. § 102(e) Over Demirjian

In the Office Action at pages 6-7, the Examiner has maintained the rejection of claims 78-83, 86-89, 93-98, 102-119, 122-125, 129-134, 138-150, 159-165, 168-170 and 172-186 under 35 U.S.C. § 102(e), as being anticipated by Demirjian *et al.*, U.S. Patent No. 5,981,177 (hereinafter "Demirjian"). Applicants respectfully traverse this rejection. The Examiner contends that Demirjian discloses mixing a first and second nucleic acid with a recombination protein to recombine the first and second nucleic acids to form a third nucleic acid, thereby forming an operably liked, functional gene from the first and second portions of the gene. The Examiner indicates that the first and second portions of the gene may be fragments of the gene and may comprise a promoter. The Examiner further contends that the gene may encode a selectable antibiotic marker. Applicants respectfully traverse these contentions.

Present claim 78 (and hence claims 79-83, 86-89, 93-98, 102-114 that depend ultimately therefrom and that are also rejected over Demirjian) recites a method of producing a nucleic acid molecule, comprising: providing a first nucleic acid molecule comprising a first portion of an antibiotic resistance gene and at least a first recombination site; providing a second nucleic acid molecule comprising a second portion of the antibiotic resistance gene and at least a second recombination site; and forming a mixture between the first and second nucleic acid molecules and at least one recombination protein, under conditions sufficient to cause recombination between the first and second recombination sites, thereby producing a third nucleic acid molecule in which the first and second portions of the gene are operably linked to form a functional antibiotic resistance gene.

Present claim 115 (and hence claims 116-119, 122-125, 129-134 and 138-150 that depend ultimately therefrom and that are also rejected over Demirjian) recites a method of producing a nucleic acid molecule, comprising: providing a first nucleic acid molecule comprising at least one promoter and at least a first recombination site, providing a second nucleic acid molecule comprising at least one antibiotic resistance gene or portion thereof and at least a second recombination site; and forming a mixture between the first and second nucleic acid molecules and at least one recombination protein, under conditions sufficient to cause recombination between the first and second recombination sites, thereby producing a third nucleic acid molecule in which the promoter and the antibiotic resistance gene or portion thereof are operably linked.

Present claim 159 (and hence claims 160-165, 168-170 and 172-186 that depend ultimately therefrom and that are also rejected over Demirjian) recites a method of producing a nucleic acid molecule comprising, providing a first nucleic acid molecule comprising at least one promoter located adjacent to at least a first recombination site; providing a second nucleic acid molecule comprising at least one gene or portion thereof located adjacent to at least a second recombination site; and forming a mixture *in vitro* between said first and second nucleic acid molecules and at least one recombination protein, under conditions sufficient to cause recombination *in vitro* between said first and second recombination sites, thereby producing a third nucleic acid molecule in which said at least one promoter and said at least one gene or portion thereof are operably linked.

Under 35 U.S.C. § 102, a claim can only be anticipated if every element in the claim is expressly or inherently disclosed in a single prior art reference. *See Kalman v. Kimberly*

Clark Corp., 713 F.2d 760, 711 (Fed.Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984). Applicants submit that the Mu transposition system disclosed in Demirjian does not entail the formation of a mixture with at least one recombination protein as recited in present claims 78, 115 and 159. In fact, the system disclosed by Demirjian does not require the use of recombination proteins whatsoever for transposition. The Examiner is directed to Demirjian at column 2, lines 57-65, which discloses the high frequency transposition and random integration of the Mu transposon in the absence of a recombination protein. Applicants further note that Demirjian discloses the use of a temperature-sensitive Mu repressor to "prevent unwanted transposition," as Mu transpostion occurs in a highly random fashion, without any recombination protein present (*see* Demirjian, Example 6 at column 23, lines 50-63). Applicants therefore respectfully submit that Demirjian clearly does not disclose the presently claimed methods of producing nucleic acid molecules that comprise forming a mixture between a first and second nucleic acid molecule and at least one recombination protein. Therefore, Demirjian does not disclose every element of the present invention, and in view of *Kalman*, Demirjian cannot and does not anticipate the present invention. Reconsideration and withdrawal of the rejection of claims 78-83, 86-89, 93-98, 102-119, 122-125, 129-134, 138-150, 159-165, 168-170 and 172-186 under 35 U.S.C. § 102(e) over Demirjian are respectfully requested.

V. The Objection Under 37 C.F.R. § 1.75(c)

In the office action at page 8, the Examiner has objected to claim 219 under 37 C.F.R. § 1.75(c), for allegedly failing to further limit the subject matter of a previous claim. The amendment to claim 219 noted above has been made to provide the proper dependency for this claim. In view of the forgoing amendments, the objection to claim 219 has been accommodated, and reconsideration and withdrawal thereof are respectfully requested.

VI. The Rejection Under 35 U.S.C. § 112, Second Paragraph

In the Office Action at pages 8-9, the Examiner has rejected claims 69, 141, 211 and 212 under 35 U.S.C. § 112, second paragraph, for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse this rejection.

The Examiner has rejected claims 69 and 141, stating that they contain the trademark/trade name "PCR" and therefore do not comply with the requirements of 35 U.S.C. § 112, second paragraph. By the foregoing amendments, claims 69 and 141 have been amended to recite "amplification product," which conveys a clear meaning in the present context without the use of a trademark. Hence, this portion of the rejection has been accommodated, and reconsideration and withdrawal of the rejection of claims 69 and 141, therefore are respectfully requested.

The Examiner has next rejected claim 211 (and hence claim 212 that depends ultimately therefrom), asserting that there is insufficient antecedent basis for the phrase "said

nucleic acid molecule" in claim 187, from which claim 211 depends. Applicants respectfully traverse this rejection. However, solely to expedite allowance of this application, claim 211 has been amended to recite "said third nucleic acid molecule," which is recited in claim 187. Hence, this portion of the rejection has been accommodated, reconsideration and withdrawal therefore are respectfully requested.

VII. The Rejection Under 35 U.S.C. § 102(b) Over Peakman

In the Office Action at pages 9-10, the Examiner has rejected claims 35, 40-46, 59-61, 66-68, 70, 71, 159, 163-167, 170, 171 and 176-179 under 35 U.S.C. § 102(b) as being anticipated by Peakman *et al.*, EP 0 542 466 (hereinafter "Peakman"). Applicants respectfully traverse this rejection.

As noted above, present claim 35 (and hence, claims 40-46, 59-61, 66-68, 70 and 71 that depend ultimately therefrom and that are also rejected over Peakman) and present claim 159 (and hence claims 163-167, 170, 171 and 176-179 that depend ultimately therefrom and that are also rejected over Peakman) recite methods of producing a nucleic acid molecule wherein, respectively, a first gene and a second gene or portions thereof, or a promoter and at least one gene or portion thereof, are operably linked to form a functional gene.

The Examiner contends that Peakman discloses a method of producing a nucleic acid molecule by providing a first nucleic acid molecule comprising a first portion of a gene and a recombination site, a second nucleic acid molecule comprising a second portion of a gene

and a recombination site, mixing *in vitro*, the first and second nucleic acids with a recombination protein to recombine the first and second nucleic acids to form a third nucleic acid thereby forming an operably linked, functional gene from the first and second portions of the gene. The Examiner further contends that the gene may encode a selectable marker. Applicants respectfully traverse these contentions.

Applicants respectfully submit that Peakman does not disclose recombination between a first nucleic acid molecule and a second nucleic acid molecule to produce *operably* linked first and second gene components. There is no indication in Peakman that both the first and second nucleic acid components involved in the recombination process comprise genes, that when linked via recombination to form a third nucleic acid molecule, will form an operably linked, functional gene, as is required by the present invention. Applicants further submit that Peakman does not disclose the production of a third nucleic acid molecule in which a promoter and a gene have been operably linked via recombination.

Applicants therefore respectfully submit that Peakman does not disclose every element of claim 35 or claim 159 (and hence the dependent claims noted above). Hence, in view of *Kalman*, Peakman cannot and does not anticipate the presently claimed invention. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) over Peakman are respectfully requested.

VIII. The Rejection Under 35 U.S.C. § 103(a) Over Johnson in view of Demirjian and Peakman

In the Office Action at pages 10-15, the Examiner has rejected claims 35-225 under 35 U.S.C. § 103(a) as being unpatentable over Johnson in view of Demirjian and Peakman. Applicants respectfully traverse this rejection.

The Examiner contends that Johnson discloses a method of producing a nucleic acid molecule by providing a first nucleic acid molecule comprising a first portion of a gene and a recombination site, a second nucleic acid molecule comprising a second portion of a gene and a recombination site, mixing *in vitro*, the first and second nucleic acids with a recombination protein to combine the first and second nucleic acids to firm a third nucleic acid molecule, thereby forming an operably linked, functional gene from the first and second portions of the gene. Applicants respectfully traverse these contentions. The Examiner further states that Johnson does not teach an antibiotic resistance gene, nor does Johnson teach selecting against a host cell transfected with the nucleic acid molecules in various host cells. The Examiner relies on the teachings of Demirjian and Peakman to cure these deficiencies.

As noted above, Johnson does not disclose or enable the present invention, including the *in vitro* methods of the present invention. The Examiner contends that one skilled in the art would have found motivation to combine the teachings of Johnson and Demirjian to produce an operably linked antibiotic resistance gene. Applicants respectfully disagree with this contention. In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a prima facie case of obviousness based upon the prior art. *See In re Piasecki*, 223 USPQ 785, 787-88 (Fed. Cir. 1984). The Examiner can satisfy this

burden only by showing some objective teaching in the prior art, or that knowledge generally available to one of ordinary skill in the art, would lead that individual to combine the relevant teachings of the references in such a way as to produce the invention as claimed, see *In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). In the present case, the Examiner's burden has not been satisfied since such a reason, suggestion, or motivation is lacking in the cited references. Absent such suggestion and motivation, the references may not be properly combined to render the claimed invention obvious.

Applicants submit one of ordinary skill would not have found the requisite motivation to combine the disclosure of Johnson and Demirjian in these references. As noted above, Demirjian discloses transposition systems that do not require recombination proteins, in contrast to those disclosed by Johnson. Hence, a report on the Mu transposition system disclosed in Demirjian would not have motivated one of ordinary skill to combine this disclosure with Johnson, which clearly requires the use of recombination proteins.

The deficiencies in Johnson and Demirjian are not cured by the disclosure of Peakman. As noted above, Peakman does not disclose operably linking two genes, nor does Peakman disclose the production of a functional, operably linked antibiotic resistance gene, either from portions of antibiotic resistance genes, or via the operable linkage of a promoter and an antibiotic resistance gene. Hence, Applicants submit that there would have been no motivation to combine the disclosures of Johnson or Demirjian with Peakman, as Peakman does not disclose the formation of operably linked genes. Applicants respectfully assert that the Examiner has not established a *prima facie* case of obviousness.

In view of the forgoing remarks, Applicants submit that Johnson, in view of Demirjian and Peakman, cannot support a *prima facie* case of obviousness. Applicants therefore respectfully request that the rejection under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

IX. Conclusion

All of the stated grounds of objection and rejection have been properly traversed. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn.

Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Brian J. Del Buono
Attorney for Applicants
Registration No. 42,473

Date: Aug. 11, 2003

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600
134,163-1